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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,122	07/07/2003	Santu Bandyopadhyay	02506.00P600.1	7170

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FITZPATRICK CELLA HARPER & SCINTO
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NEW YORK, NY 10112

EXAMINER

SOROUSH, LAYLA

ART UNIT	PAPER NUMBER
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1617

MAIL DATE	DELIVERY MODE
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04/16/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/613,122

Applicant(s)

BANDYOPADHYAY ET AL.

Examiner

LAYLA SOROUGH

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period **will** apply and **will** expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply **will**, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

The response filed December 18, 2007 presents remarks and arguments submitted to the office action mailed October 9, 2007 is acknowledged.

Applicants filing of a Terminal Disclaimer for the ODP rejection made over 10/338688 will be withdrawn once the Terminal Disclaimer is approved.

The following new rejections have been made:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for a pharmaceutical composition consisting essentially of chlorogenic acid and p-coumaric acid in a ratio ranging between 1:1 to 1:10 and at least one pharmaceutically acceptable carrier wherein the composition is adapted for treating acute and chronic myeloid leukemia in animals and humans and a method of use thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art;

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(d) the level of one of ordinary skill in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation added to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

While Applicant reasonably demonstrates a composition consisting essentially of chlorogenic acid and 3-o-p-coumaryl quinic acid in a ratio ranging between 1:1 to 1:10 and at least one pharmaceutically acceptable carrier having growth inhibitory activity against leukemic cell type K652 having utility in the treatment of myeloid leukemias, nowhere in the specification as originally drafted does Applicant disclose a pharmaceutical composition consisting essentially of chlorogenic acid and p-coumaryl quinic acid in a ratio ranging between 1:1 to 1:10 and at least one pharmaceutically acceptable carrier wherein the composition is adapted for treating acute and chronic myeloid leukemia in animals and humans and a method of use thereof. In fact, no working examples or data thereof are provided for a pharmaceutical composition consisting essentially of chlorogenic acid and p-coumaryl quinic acid and a pharmaceutically acceptable carrier which is adapted for treatment acute and myeloid leukemia in animals and humans and which is adapted for the growth inhibition of leukemic cells lines of type K562 in the present specification, much less a demonstration of a method of use thereof for treatment of acute and chronic myeloid leukemia in animals and humans, as broadly claimed by Applicant.

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The state of the art at the time the invention was made unpredictable to the administration of any and all analogs of a compound known to be useful in methods of disease conditions. For example, in a study Hou et al. (Biochemical Pharmacology, 2005; vol. 70, pp. 415-425. "*Anthocyanidins Inhibit Cyclooxygenase-2 Expression in LPS-evoked macrophages: Structure Activity Relationship and Molecular Mechanisms Involved*".) discerns that the *ortho*-dihydroxyphenyl structure on the B-ring of anthocyanidins appears to be essential for the inhibitory action of anthocyanidins on cyclooxygenase-2 (COX-2) expression because pelargonidin, peonidin and malvidin, having no such *ortho*-dihydroxyphenyl structure failed to show the inhibitory effect. In the art of chemistry, p-coumaryl quinic acids are often referred to as analogues of chlorogenic acid. In another study, Hou (Hou et al. Int J Oncol. 2003; (3):705-12. "*Anthocyanidins induce apoptosis in human promyelocytic leukemia cells: structure-activity relationship and mechanisms involved*.) tests the ability of anthocyanidins to induce apoptosis in human promyelocytic leukemic cells (HL-60) to investigate their anti-cancer or anti-leukemic effect. Hou teaches, "Of six anthocyanidins representing the aglycons of most of anthocyanins, only those with an *ortho*-dihydroxyphenyl structure on the B-ring induce apoptosis, suggesting that the *ortho*-dihydroxyphenyl structure of anthocyanidins may contribute to the induction of apoptosis." It is also known that p-coumaryl quinic acids exist as 3-O-p-coumarylquinic acid, 4-O-p-coumarylquinic acid and 5-O-p-coumarylquinic acid, for example. Thus, given such differences in the molecular structure of such p-coumaryl quinic acids and in the absence of a showing that the structural disparity between any and all p-coumaryl quinic acids exhibit the same functional effect for inhibition of growth leukemic cell lines of cell type K562 in either an *in vitro* or *in vivo* test model it is not reasonable to predict that a the claim-designated composition comprising any and all p-coumaryl quinic acids would

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provide the same beneficial functional effect for the treatment of acute and chronic myeloid leukemia in animals and humans. Even Applicant appears to readily admit that the molecular structure of chlorogenic acid lends additional bioactive activity over 3-p-coumaryl quinic acid:

[0083] Structure filed for patent earlier was 3-p-coumaryl quinic acid which showed CD33 + myeloid cells destruction but not CD33 - cells, and this is very similar to chlorogenic acid. Except the additional hydroxyl group at C-3 position of the aromatic ring in chlorogenic acid other structures are precisely similar. Therefore, the additional activity of chlorogenic acid over the 3-p-coumaryl quinic acid can be suggested to be due to the presence of hydroxyl group at C-3 position of aromatic ring. This specific difference has given broader and stronger activity to Chlorogenic acid in destroying both CD33 - and CD33 + cells and also lymphoid leukemic cells.

In view of the breadth of the claims and the lack of guidance provided by the specification, the lack of working examples, as well as the unpredictability of the art, it would take undue experimentation without a reasonable expectation of success for the skilled artisan to make and/or use the instantly claimed method, as broadly claimed by Applicant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuroda et al. (Mutation Research/Reviews in Mutation Research Volume 436, Issue 1,

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January 1999, Pages 69-97) in view of Yang et al. (Drug Metabolism Reviews, Volume 33, Issue 3 & 4 December 2001 , pages 237 – 253).

Kuroda et al. teaches “the antimutagenic activity against various mutagens of tea extracts [green and black teas] and polyphenols including ECG and EGCG has been demonstrated in microbial systems_ *Salmonella typhimurium* and *Escherichia coli*, mammalian cell systems and in vivo animal tests. The anticarcinogenic activity of tea phenols has been shown in experimental animals such as rats and mice, in transplantable tumors, carcinogen-induced tumors in digestive organs, mammary glands, hepatocarcinomas, lung cancers, skin tumors, leukemia, tumor promotion and metastasis.” Green tea will comprise a carrier (i.e. water) therefore meeting the limitation of claim 4.

Kuroda et al. fails to teach the polyphenols of the black and green tea, the amount ratio of CA and PCQ, mode of administration, dose levels administered, the percentage growth inhibition as claimed.

Yang et al. teaches polyphenols of black and green teas are inclusive of chlorogenic acid and quinic acid. Such teas are useful in prevention of carcinogenesis.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat cancers inclusive of acute, chronic and lymphoid leukemias with a composition comprising chlorogenic acid and coumarylquinic acid. The motivation to treat cancers inclusive of leukemias is from the teaching of Kuroda et al. that “the antimutagenic activity against various mutagens of tea extracts [green and black teas] and polyphenols including ECG and EGCG has been demonstrated in microbial

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systems_ *Salmonella typhimurium* and *Escherichia coli*, mammalian cell systems and in vivo animal tests. The anticarcinogenic activity of tea phenols has been shown in experimental animals such as rats and mice, in transplantable tumors, carcinogen-induced tumors in digestive organs, mammary glands, hepatocarcinomas, lung cancers, skin tumors, leukemia, tumor promotion and metastasis;" and Yang et al. that polyphenols of black and green teas are inclusive of chlorogenic acid and quinic acid. Such teas are useful in prevention of carcinogenesis. Hence a skilled artisan would have reasonable expectation of successfully treating acute, chronic and lymphoid leukemias with the same efficacy and results.

Additionally, the determination of optimal or workable, amount ratio, mode of administration, dose levels administered, of the CA and PCQ by routine experimentation is obvious absent showing of criticality of the claimed amount ratio, mode of administration, or dose levels administered. One having ordinary skill in the art would have been motivated to do this to obtain are deemed to obtain the best possible pharmaceutical results. The skilled artisan would have reasonable expectation of successfully producing a composition with good efficacy and results in treating the acute, chronic and lymphoid leukemias. With respect to the percentage growth inhibition of the leukemic cells, the observation of the specific inhibition percentages that would have resulted from practicing the methods taught by Kuroda et al. is a matter that does not impart patentable moment to the claimed subject matter. One of ordinary skill in the art, by virtue of the very teaching that the compounds are effective for the treatment of leukemia, would have been imbued with at least a reasonable expectation that the

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growth of cells associated with leukemia would have been inhibited to some degree and the determination of the percentage inhibition for the compounds would have been a matter well within the purview of the skilled artisan.

The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). “A consisting essentially of’ claim occupies a middle ground between closed claims that are written in a consisting of’ format and fully open claims that are drafted in a comprising’ format.” PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, “the consisting essentially of” language in the claim is treated as “comprising” language and it is an applicant’s burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of’ language.” (See MPEP 2111.03)

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferguson (Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis; Vol 475, Issues 1-2, 18 April 2001, Pages 89-111).

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Ferguson teaches green tea extract comprises polyphenols such as epigallocatechin gallate, chlorogenic acid and coumarylquinic acid (p 90 col 2).

“Epidemiological studies correlating the intake of various polyphenol sources, using both cohort or case-control studies have been generally suggestive that green tea, red wine and more generally flavonoid intake may protect against diseases, especially cardiovascular disease and cancer. It also appears that increasing green tea intake can decrease the recurrence rate of breast cancer, as well as slowing the development of this cancer (p102).”

The reference does not teach the method of treating acute and chronic leukemia and lymphoid leukemia, the additives, the amount ratio of CA and PCQ, mode of administration, dose levels administered, the percentage growth inhibition as claimed.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat cancers inclusive of leukemias with a composition comprising chlorogenic acid and coumarylquinic acid. The motivation to treat cancers inclusive of leukemias is from the teaching of Ferguson that “Epidemiological studies correlating the intake of various polyphenol sources, using both cohort or case-control studies have been generally suggestive that green tea, red wine and more generally flavonoid intake may protect against diseases, especially cardiovascular disease and cancer. It also appears that increasing green tea intake can decrease the recurrence rate of breast cancer, as well as slowing the development of this cancer (p102).” Hence a skilled

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artisan would have reasonable expectation of successfully treating any cancer with the same efficacy and results.

Additionally, the determination of optimal or workable, amount ratio, mode of administration, dose levels administered, of the CA and PCQ by routine experimentation is obvious absent showing of criticality of the claimed amount ratio, mode of administration, or dose levels administered. One having ordinary skill in the art would have been motivated to do this to obtain are deemed to obtain the best possible pharmaceutical results. The skilled artisan would have reasonable expectation of successfully producing a composition with good efficacy and results in treating the acute, chronic and lymphoid leukemias. With respect to the percentage growth inhibition of the leukemic cells, the observation of the specific inhibition percentages that would have resulted from practicing the methods taught by Kuroda et al. is a matter that does not impart patentable moment to the claimed subject matter. One of ordinary skill in the art, by virtue of the very teaching that the compounds are effective for the treatment of leukemia, would have been imbued with at least a reasonable expectation that the growth of cells associated with leukemia would have been inhibited to some degree and the determination of the percentage inhibition for the compounds would have been a matter well within the purview of the skilled artisan.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). "A consisting essentially of" claim occupies a middle

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ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For art purposes, "the consisting essentially of" language in the claim is treated as "comprising" language and it is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by consisting essentially of' language." (See MPEP 2111.03)

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (Drug Metabolism Reviews, Volume 33, Issue 3 & 4 December 2001 , pages 237 – 253).

Yang et al. teaches polyphenols of black and green teas are inclusive of chlorogenic acid and quinic acid. Such teas are useful in prevention of carcinogenesis. Green tea will comprise a carrier (i.e. water) therefore meeting the limitation of claim 4.

The reference does not teach the method of treating acute and chronic leukemia and lymphoid leukemia, the additives, the amount ratio of CA and PCQ, mode of administration, dose levels administered, the percentage growth inhibition as claimed.

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It would have been obvious to one of ordinary skill in the art at the time of the invention to treat cancers inclusive of the genus leukemias with a composition comprising chlorogenic acid and coumarylquinic acid. The motivation to treat cancers inclusive of leukemias is from the teaching of Yang et al that "are useful in prevention of carcinogenesis." Hence a skilled artisan would have reasonable expectation of successfully treating any cancer with the same efficacy and results.

Additionally, the determination of optimal or workable, amount ratio, mode of administration, dose levels administered, of the CA and PCQ by routine experimentation is obvious absent showing of criticality of the claimed amount ratio, mode of administration, or dose levels administered. One having ordinary skill in the art would have been motivated to do this to obtain are deemed to obtain the best possible pharmaceutical results. The skilled artisan would have reasonable expectation of successfully producing a composition with good efficacy and results in treating the acute, chronic and lymphoid leukemias. With respect to the percentage growth inhibition of the leukemic cells, the observation of the specific inhibition percentages that would have resulted from practicing the methods taught by Kuroda et al. is a matter that does not impart patentable moment to the claimed subject matter. One of ordinary skill in the art, by virtue of the very teaching that the compounds are effective for the treatment of leukemia, would have been imbued with at least a reasonable expectation that the growth of cells associated with leukemia would have been inhibited to some degree and the determination of the percentage inhibition for the compounds would have been a matter well within the purview of the skilled artisan.

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Response to Arguments

Applicant's arguments filed on December 18, 2007 have been considered.

Applicant's arguments with respect to claims 1-17 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No Claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617